

REMARKS

Claims 1,3-13, 20-21, 25 and 26 are currently pending in the application. Claim 1 has been amended to add the limitation that the claimed method amplifies the population of RNA in a manner that preserves the relative abundance of individual nucleic acid species. Support for this amendment may be found, for example, on page 1, lines 14-16. Claim 1 has also been amended to add the limitation that following second strand cDNA synthesis at 16°C for at least about 2 hours the reaction is heated to 75°C for at least 1 min. Support for this amendment to claim 1 may be found on page 13, lines 30-31 and page 14, lines 1-3.

Non-statutory Double Patenting

The examiner has maintained the provisional obviousness-type double patenting rejection of claim 5-8, 10-22 as being unpatentable over U.S patent no. 6,582,906. Applicants have filed a terminal disclaimer herewith.

Obviousness rejection under 35 U.S.C. 103(a)- Sooknanan et al in view of Van Gelder et al. and Mak

The Examiner rejected Claims 1, 3-13, 25-26 under 35 U.S.C. 103 (a) over Sooknanan *et al.* (WO96.17076) in view of Van Gelder *et al.* (5,545,522) and Mak (6,190,691).

Claim 1 has been amended to add the limitation that the reaction is subjected to heating to 75°C for at least one minute before the step of synthesizing multiple copies of RNA. Neither Sooknanan *et al.*, Van Gelder *et al.* nor Mak teach heating to 75°C

between synthesis of double stranded cDNA and synthesis of RNA. In view of the amendments applicants respectfully request that the rejection be removed.

In addition, the mere fact that references can be combined does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. Furthermore, one of skill in the art would need to understand that the modification to arrive at the claimed subject matter can be made with a *reasonable expectation of success*. Based on the teachings of Sooknanan *et al.*, Van Gelder *et al.* and Mak as a whole, one of skill in the art would not have a reasonable expectation of success using the techniques of Van Gelder *et al.* and Mak to modify the teachings of Sooknanan *et al.*

Applicant's claims are directed at a method of amplifying a population of nucleic acid using four sequential steps that are performed in a single tube (without extraction and precipitation) and with serial addition of reagents, including enzymes and buffers, with preservation of the relative abundance of individual nucleic acid species.

Sooknanan *et al.* is a method for amplifying a specific RNA in a single reaction where all steps take place simultaneously under identical reaction conditions in a single vessel.

Van Gelder *et al.* teaches a method of amplifying a population of mRNA, but does not teach that the reaction is performed in a single vessel. Mak is cited for teaching stepwise addition of reagents.

Applicant's method provides different buffer conditions for each step, recognizing that different enzymes function optimally under different conditions. Sooknanan *et al.* sacrifices optimal enzyme function for ease of use and simplicity. For example, on page 43 lines 16-22 of the Sooknanan *et al.* specification they report that the method provides amplification levels that are 34.5% of the levels provided by a second protocol, NASBA.

While it is not unexpected that the method of Sooknanan *et al.* can be used to detect the presence of a single specific RNA, one of skill in the art would not have expected that the method could be modified according to the teachings of Van Gelder *et al.* and Mak to detect the relative levels of many different RNAs present in varying abundances.

The purpose of the Applicant's presently claimed invention is amplification of a population of nucleic acids in a manner that is efficient, reproducible and preserves the relative abundance of individual species. A total RNA sample from humans, for example, may have more than 30,000 different species of transcripts to be amplified. The purpose of the Sooknanan *et al.* invention is to eliminate the need for serial additions of reagents and varying temperature steps. A researcher would not have had a reasonable expectation that the Sooknanan method, with its reduced efficiency of amplification, would provide reproducible and efficient amplification of many different RNAs that are present in different amounts with preservation of relative amounts of individual species.

Applicants respectfully request that the rejection of claims 1, 3-13, 25-26 under 35 U.S.C. §103(a) be reconsidered and withdrawn.

Obviousness rejection under 35 U.S.C. 103(a)- Sooknanan et al in view of Van Gelder et al., Mak and further in view of Schnipelsky et al. (5,229,297)

Claims 20-21 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Sooknanan *et al.* (WO96.17076) in view of Van Gelder *et al.* (5,545,522) and Mak (6,190,691) as applied to claims 1 and 3-13 above, and further in view of Schnipelsky *et al.* (5,229,297).

For the reasons indicated above, claim 1 as amended, is not anticipated by Sooknanan *et al.*, Van Gelder *et al.* and Mak and Schnipelsky *et. al.* fails to remedy the deficiencies of the cited references as applied to claims 20 and 21.

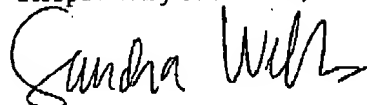
For these reasons and the reasons set forth *supra*, Applicants respectfully request that the rejection of claims 20-21 under 35 U.S.C. §103(a) be reconsidered and withdrawn.

CONCLUSION

For these reasons, Applicants believe all pending claims are now in condition for allowance and should be passed to issue. If the Examiner feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at (408) 731-5768.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account 01-0431.

Respectfully submitted,



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